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Travel-Associated Zika Virus Disease Acquired in the Americas Through February 2016

A GeoSentinel Analysis

Davidson H. Hamer, MD; Kira A. Barbre, MPH; Lin H. Chen, MD; Martin P. Grobusch, MD, PhD; Patricia Schlagenhauf, PhD; Abraham Goorhuis, MD, PhD; Perry J.J. van Genderen, MD, PhD; Israel Molina, MD, PhD; Hilmir Asgeirsson, MD, PhD; Phyllis E. Kozarsky, MD; Eric Caumes, MD; Stefan H. Hagmann, MD, MSc; Frank P. Mockenhaupt, MD; Gilles Eperon, MD; Elizabeth D. Barnett, MD; Emmanuel Bottieau, MD, PhD; Andrea K. Boggild, MSc, MD; Philippe Gautret, MD, PhD; Noreen A. Hynes, MD, MPH; Susan Kuhn, MD; R. Ryan Lash, MA; Karin Leder, MBBS, MPH, PhD; Michael Libman, MD; Denis J.M. Malvy, MD, PhD; Cecilia Perret, MD; Camilla Rothe, MD; Eli Schwartz, MD; Annelies Wilder-Smith, MD, PhD, MIH; Martin S. Cetron, MD; and Douglas H. Esposito, MD, MPH; for the GeoSentinel Surveillance Network*

Background: Zika virus has spread rapidly in the Americas and has been imported into many nonendemic countries by travelers.

Objective: To describe clinical manifestations and epidemiology of Zika virus disease in travelers exposed in the Americas.

Design: Descriptive, using GeoSentinel records.

Setting: 63 travel and tropical medicine clinics in 30 countries.

Patients: Ill returned travelers with a confirmed, probable, or clinically suspected diagnosis of Zika virus disease seen between January 2013 and 29 February 2016.

Measurements: Frequencies of demographic, trip, and clinical characteristics and complications.

Results: Starting in May 2015, 93 cases of Zika virus disease were reported. Common symptoms included exanthema (88%), fever (76%), and arthralgia (72%). Fifty-nine percent of patients were exposed in South America; 71% were diagnosed in Europe. Case status was established most commonly by polymerase chain reaction (PCR) testing of blood and less often by PCR testing of other body fluids or serology and plaque-reduction neutralization testing. Two patients developed Guillain–Barré syndrome, and 3 of 4 pregnancies had adverse outcomes (microcephaly, major fetal neurologic abnormalities, and intrauterine fetal death).

Limitation: Surveillance data collected by specialized clinics may not be representative of all ill returned travelers, and denominator data are unavailable.

Conclusion: These surveillance data help characterize the clinical manifestations and adverse outcomes of Zika virus disease among travelers infected in the Americas and show a need for global standardization of diagnostic testing. The serious fetal complications observed in this study highlight the importance of travel advisories and prevention measures for pregnant women and their partners. Travelers are sentinels for global Zika virus circulation and may facilitate further transmission.

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For author affiliations, see end of text.

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* For a list of additional members of the GeoSentinel Surveillance Network who contributed data, see the **Appendix** (available at www.annals.org).

Zika virus has spread rapidly throughout Latin America and the Caribbean since its initial identification in the Americas in Brazil in 2015 (1, 2). Although infections are asymptomatic or relatively mild in approximately 80% of persons (3), serious complications have been described, including neurologic manifestations, such as Guillain–Barré syndrome (GBS), myelitis, and encephalitis; adverse pregnancy outcomes, such as miscarriage, prematurity, and fetal neurologic complications; and, rarely, death (4–8).

Phylogenetic analyses have shown that the Asian strain of Zika virus is responsible for the epidemic in the Americas (9). Three theories of how Zika virus entered Brazil identified a key role for travelers. Two include the possible introduction through infected participants in the 2014 World Cup in Brazil and the Va'a canoe event in Rio de Janeiro in August 2014, which included participants from French Polynesia. However, a genetic analysis suggests that Zika virus may have been introduced into Brazil between May and December 2013 (10, 11), possibly during the Confederations Cup soccer tournament in June 2013.

Many case reports and small series of travelers with Zika virus disease diagnosed in Western Europe and North America have been published since the beginning of the epidemic in the Americas (12–16). The Centers for Disease Control and Prevention (CDC) recently described typical symptoms and demographic characteristics of U.S. travelers with Zika virus infection (14). Given the widespread distribution of *Aedes aegypti* and other potentially competent vectors, such as *A albopictus,* justifiable concerns have been raised about the potential for introduction of Zika virus into the continental United States and southerly areas of Europe by travelers from areas with ongoing Zika virus transmission (2, 17).

To develop a broader understanding of the extent of Zika virus disease in global travelers from the Amer-

icas and the characteristics of travel-acquired infections, we performed an analysis of Zika virus disease cases reported by the GeoSentinel Surveillance Network.

METHODS

GeoSentinel, a global surveillance network comprising 63 specialized travel and tropical medicine clinics in 30 countries, collected the data. Staffed by specialists in travel and tropical medicine, these clinics provide routine clinical care to ill travelers and contribute deidentified demographic, travel, and clinical surveillance data on patients with travel-related illnesses to a centralized database (18, 19).

GeoSentinel's data collection protocol has been reviewed by the institutional review board officer at the CDC's National Center for Emerging and Zoonotic Infectious Diseases and is classified as public health surveillance and not human subjects research. When indicated by national regulations at individual GeoSentinel sites, additional ethics clearance has been obtained.

Zika Virus Disease Diagnostic Criteria

We limited data extraction to patients diagnosed with Zika virus disease acquired in regions of the Americas (South America, Central America [including Mexico], and the Caribbean) who were evaluated at a GeoSentinel site from January 2013 to 29 February 2016. January 2013 was chosen to permit identification of cases from the earliest proposed date of introduction of Zika virus into the Americas (10, 11). Sites that contributed patient data were asked to provide supplemental information, including symptoms and signs, clinical course and outcomes of known pregnancies, clinical course of patients with GBS, hematologic results, and virologic and serologic diagnostic testing results for recent and past Zika or dengue virus infections. Testing was not standardized across sites and countries; diagnostic testing decisions were based on local and individual clinician standards and preferences and were subject to availability of methods. Using the interim case definitions from the U.S. Council of State and Territorial Epidemiologists (**Appendix Table**, available at www.annals.org) (20), 2 clinicians (D.H.H. and D.H.E.), independently and blinded to each other's determination, classified each patient as a confirmed, probable, or suspect case patient (defined as persons with travel to a country with known active Zika virus transmission and meeting the interim case definitions). Discrepancies (5% of the cases) were discussed and a final determination was made. Patients were excluded if they did not fulfill the diagnostic criteria.

Travel-Related Definitions and Classifications

Five possible GeoSentinel travel purpose designations were used in this analysis: tourism; business; missionary, volunteer, research, or aid work; visiting friends and relatives; and planned medical care (19). GeoSentinel does not collect data on specific activities of travelers beyond the standard "purpose of travel" definitions. Country of exposure was determined by the evaluating clinician only when ascertainable and was based on travel itinerary, Zika virus disease epidemiology, and incubation periods. When a traveler visited multiple countries within the incubation period of Zika virus, the exact country could not be defined, so region of exposure was provided instead.

Data Management and Analysis

Data were managed in a structured query language database. Descriptive analyses were conducted using SAS, version 9.3 (SAS Institute). Time to clinic presentation was calculated as the number of days between the reported date of symptom onset and the date of the first visit to the GeoSentinel clinic. Maps were created using ArcGIS 10.3.1 (Esri).

Role of the Funding Source

GeoSentinel, the Global Surveillance Network of the International Society of Travel Medicine (ISTM), is supported by a cooperative agreement from the CDC. The ISTM and the Public Health Agency of Canada also provide funds for GeoSentinel. CDC staff participated in the design, collection, analysis, and interpretation of data and the writing of the manuscript.

RESULTS

Among 102 patients reported to GeoSentinel with a diagnosis of Zika virus disease between 1 January 2013 and 29 February 2016, there were 64 confirmed, 13 probable, and 16 clinically suspect cases; 9 patients not meeting diagnostic criteria were excluded. Of the 93 cases, the first was reported in May 2015, followed by 2 reported in November 2015. The number of cases then increased rapidly and steadily, with 20 cases reported in December 2015, 32 reported in January 2016, and 38 reported in February 2016.

Of the 93 case patients, 62% were female (**Table 1**); median age was 41 years (range, 3 to 77 years), and three quarters were aged 20 to 59 years. Major reasons for travel included tourism (49%), visiting friends and relatives (39%), and business (8%). Regions of Zika virus exposure were South America (59%), the Caribbean (25%), and Central America (16%). The top 5 countries where Zika virus disease were acquired were Suriname (22%), Colombia (17%), Brazil (11%), Martinique (11%), and Venezuela (8%). The median duration of travel to the country of exposure was 22 days (range, 3 to 378 days [87 patients]). Diagnoses were made at GeoSentinel sites in Western Europe (71%), North America (17%), the Middle East (9%), and South America (3%). The country of exposure and country of diagnosis are shown in **Figure 1**. The median time from symptom onset to clinic presentation was 6 days (range, 1 to 65 days [84 patients]) overall, 5.5 days (range, 1 to 65 days [58 patients]) for confirmed cases, 9 days (range, 3 to 52 days [13 patients]) for probable cases, and 7 days (range, 1 to 19 days [13 patients]) for suspect cases.

Of the 93 case patients, 72 had polymerase chain reaction (PCR) testing done on at least 1 body fluid. Of these, 57 were classified as confirmed case patients based on positive PCR results. Virus RNA was detected

in blood alone in 30 patients, in urine alone in 10 patients, in blood and urine in 12 patients, in urine and saliva in 2 patients, in urine and semen in 1 patient, and in semen alone in 2 patients. Of note, among 9 confirmed case patients with a negative blood PCR result, 5 tested positive in urine only, 2 tested positive in semen only, 1 tested positive in urine and semen, and 1 tested positive in urine and saliva. An additional 7 cases were confirmed by plaque-reduction neutralization testing with a Zika–dengue virus ratio of at least 4 (2 of the 7 also had blood PCR performed, with negative results); all such diagnoses were made in North America. Data on the precise timing from symptom onset to diagnostic sample collection were not collected.

Eighty-nine patients (96%) were managed as outpatients. Exanthema was the most common sign or symptom (88%), followed by fever (76%), arthralgia (72%), headache (61%), myalgia (60%), fatigue (47%), conjunctivitis (40%), and pruritus (23%) (Figure 2). All but 1 patient with pruritus had exanthema, and one third (7 of 21) described the itching as severe. Less common findings included nausea, diarrhea, arthritis (predominantly of the peripheral joints, including the ankles, feet, and hands), paresthesias, dysgeusia, and sore throat or pharyngitis. No deaths were reported.

Of 4 pregnant women, 1 with infection acquired in the second trimester delivered a healthy newborn who, at age 2 months, seemed neurologically healthy (Table 2) (21, 22). The remaining 3 women had confirmed Zika virus disease that occurred in the first trimester, and all had pregnancy complications. Two patients, both confirmed case patients, had GBS (Table 2) (16).

Hematologic results were available for 75 of 93 (81%) case patients. The median leukocyte count (74 patients) was 5.6 × 10^9 cells/L (range, 2.8 to 14.5 × 10^9 cells/L), median hemoglobin level (73 patients) was 133 g/L (range, 70 to 162 g/L), and median platelet count (75 patients) was 221 × 10^9 cells/L (range, 10 to 515 × 10^9 cells/L). Seventeen patients (23%) were leukopenic (leukocyte count <4.5 × 10^9 cells/L), 28 (38%) were anemic (hemoglobin level <135 g/L [male] or <120 g/L [female]), and 4 (5%) were thrombocytopenic (platelet count <150 × 10^9 cells/L). One patient had immune-mediated thrombocytopenia and a nadir platelet count of 10 × 10^9 cells/L, which responded quickly to intravenous immunoglobulin therapy (23, 24).

Table 1. Demographic and Travel Characteristics of 93 Patients With Zika Virus Disease Acquired in the Americas Who Were Evaluated at GeoSentinel Sites Through February 2016*

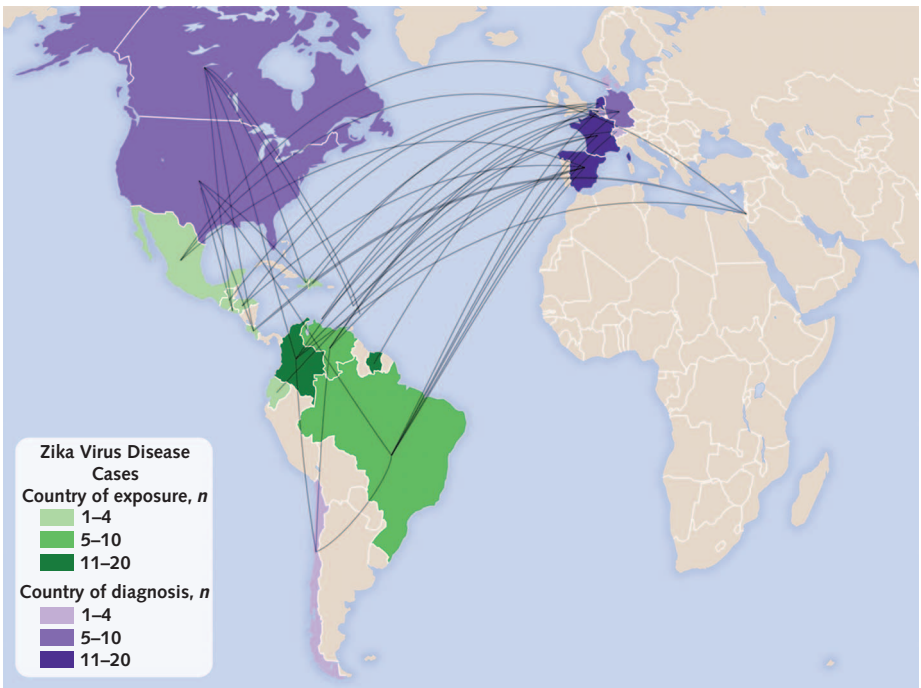
Characteristic	Patients, *n* (%)
Female	58 (62)
Age†	
<20 y	8 (9)
20–39 y	36 (39)
40–59 y	33 (36)
≥60 y	15 (16)
Reason for travel	
Tourism	46 (49)
Visiting friends and relatives	36 (39)
Business/corporate/conference	7 (8)
Missionary/volunteer/research/aid work	3 (3)
Planned medical care	1 (1)
Region and country of exposure	
South America	55 (59)
Suriname	20 (22)
Colombia	16 (17)
Brazil	10 (11)
Venezuela	7 (8)
Ecuador	1 (1)
Unascertainable	1 (1)
Caribbean	23 (25)
Martinique	10 (11)
Haiti	4 (4)
Dominican Republic	2 (2)
Guadeloupe	2 (2)
Netherlands Antilles	2 (2)
Barbados	1 (1)
Unascertainable	2 (2)
Central America	15 (16)
Honduras	3 (3)
Mexico	3 (3)
Costa Rica	3 (3)
El Salvador	3 (3)
Guatemala	1 (1)
Unascertainable	2 (2)
Region (country) of diagnosis	
Western Europe	66 (71)
The Netherlands	22 (24)
Spain	16 (17)
France	14 (15)
Germany	7 (8)
Belgium	4 (4)
Switzerland	2 (2)
Denmark	1 (1)
North America	16 (17)
United States	8 (9)
Canada	8 (9)
Middle East	
Israel	8 (9)
South America	
Chile	3 (3)

* Percentages may not sum to totals due to rounding.
† Missing for 1 patient (*n* = 92).

DISCUSSION

This case series of Zika virus disease in returning travelers reveals clinical manifestations similar to those reported from other areas with outbreaks, including Yap, French Polynesia, Brazil, and Puerto Rico, with the main symptoms being exanthema, fever, arthritis or arthralgia, myalgia, conjunctivitis, and fatigue (3, 12, 25, 26). Overall, Zika virus disease was mild, with most patients managed on an outpatient basis. Exanthema, usually maculopapular, has occurred in 74% to 97% of patients with Zika virus infection and has been described in all published case series (3, 12, 25, 26). Of note, pruritus, often described as severe, was reported in 79% of cases from Rio de Janeiro, Brazil (25) but in

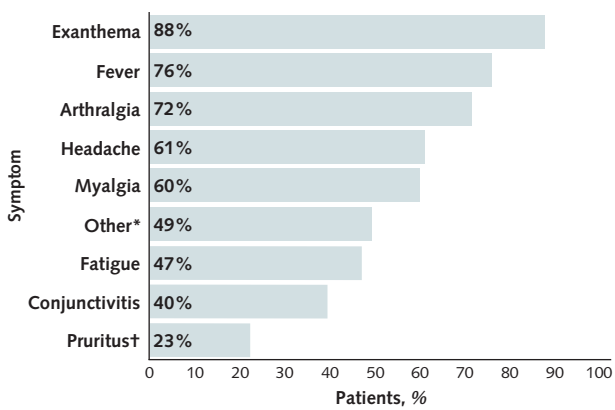
Figure 1. Country of Zika virus exposure and disease diagnosis.



Lines represent travel routes, with the origin and terminus of each line meant to show country only; lines are not representative of the exact location of exposure or the exact GeoSentinel site where the diagnosis was made.

only 23% of our case patients. However, this information was not systematically collected in our series but was provided in the form of a discretionary comment; thus, our reported frequency of pruritus may be an underestimate. Likewise, fatigue was reported frequently in French Polynesia (78%) and Brazil (73%) but not in Yap or Puerto Rico, possibly because it was not systematically documented in the latter 2 series. We observed a lower frequency of retro-orbital pain (1%) and edema or swelling (8%) than in other reports (3, 25), although, as with pruritus, we did not systematically assess these symptoms.

Figure 2. Clinical symptoms and signs among 93 patients diagnosed with Zika virus disease acquired in the Americas.



* 46 persons reported a total of 71 additional symptoms and signs in the form of comments in this category. Those observed in ≥3 patients (≥3%) included diarrhea (12%), joint swelling/arthritis (9%), abdominal pain (8%), nausea (6%), anorexia (4%), retro-orbital pain (3%), pharyngitis (3%), and dysgeusia (3%).
† Data were not collected systematically.

We identified several patients with severe adverse outcomes associated with Zika virus disease, including pregnancy complications and GBS. In addition, we noted a rare but potentially life-threatening Zika virus–associated complication of immune-mediated thrombocytopenia that was not associated with concomitant dengue or chikungunya infection (23, 24). Referral bias, with more symptomatic patients and complicated disease at GeoSentinel sites, may explain the relatively high proportion of major complications in our case series (4, 27, 28).

Three pregnant travelers in this analysis with Zika virus disease acquired during the first trimester had severe fetal complications, including intrauterine fetal death and major fetal neurologic complications that resulted in elective termination of pregnancy in 1 patient. The global concern and urgency surrounding Zika virus–associated congenital malformations, for which evidence for causality now exists (6), has defined the Zika virus outbreak in the Americas since its inception and is the likely source of the preponderance of women we identified with Zika virus disease, given that female travelers are more likely to be tested than male travelers. A causal link has been established between Zika virus infection in pregnancy and fetal microcephaly and other serious brain defects (6), and infection in the

Table 2. Characteristics of Patients With Zika Virus Infection Associated With Pregnancy and Guillain–Barré Syndrome

Patient	Reference	Country of Exposure	Country of Diagnosis	Reason for Travel	Diagnostic Category	Presenting Symptoms and Clinical History	Final Outcome
Pregnancy*							
33-year-old woman	21	Belize, Guatemala, and Mexico	United States	Tourism	Confirmed (ZPRNT–DPRNT ≥4; PCR not done)	Fever, exanthema, myalgia, headache, and conjunctivitis in the first trimester. Major fetal neurologic abnormalities, including ventriculomegaly, brain atrophy, and agenesis of the corpus callosum.	Elective termination of pregnancy; amniotic fluid PCR-positive for Zika virus
31-year-old woman	22	Suriname	The Netherlands	Visiting friends and relatives	Confirmed (blood and urine PCR-positive for Zika virus)	Exanthema, arthralgia, headache, and fatigue, with symptom onset in the first trimester.	Intrauterine fetal death, with fetal tissue PCR-positive for Zika virus
35-year-old woman	–	Colombia	Spain	Tourism	Probable (positive for Zika virus IgM antibodies; positive ZPRNT result; negative for dengue virus IgM antibodies; blood, amniotic fluid, and urine PCR-negative for Zika virus; DPRNT not done)	Exanthema, arthralgia, and fatigue, with symptom onset in the second trimester (25 weeks' gestation).	Normal delivery of neurologically healthy infant (status 2 mo after delivery)
41-year-old woman	–	Colombia	Spain	Visiting friends and relatives	Confirmed (blood and amniotic fluid PCR-positive for Zika virus)	Fever, exanthema, headache, and fatigue, with symptom onset in the first trimester. Initially normal results on fetal ultrasonography, but follow-up ultrasonography revealed microcephaly.	Patient elected to complete her pregnancy
Guillain-Barré syndrome*							
35-year-old man	16	Haiti	United States	Planned medical care	Confirmed (ZPRNT–DPRNT ≥4; PCR not done)	No symptoms of Zika virus infection. Presented with dysarthria, facial weakness, ophthalmoplegia, lower extremity weakness, and sensory deficits. Treated with intravenous IgG.	Nearly full recovery other than persistent left facial weakness
60-year-old woman	–	Suriname	The Netherlands	Tourism	Confirmed (serum and urine PCR-positive for Zika virus; cerebrospinal fluid negative)	Fever, myalgia, diarrhea, vomiting, and unsteady gait. Subsequently developed progressive global weakness of arms and legs combined with bulbar dysarthria with diplegia facialis and sensory loss (sense of touch and vibration) of both feet and absent tendon reflexes. Electromyogram showed demyelinating polyneuropathy.	Improved speech, facial nerve paresis, and limb muscle weakness; incomplete recovery

DPRNT = plaque-reduction neutralization testing for antibodies to dengue virus; PCR = polymerase chain reaction; ZPRNT = plaque-reduction neutralization testing for antibodies to Zika virus; ZPRNT–DPRNT = Zika–dengue virus ratio by plaque-reduction neutralization testing.
* Arranged chronologically by date of presentation.

first trimester is most strongly associated with risk for these complications (27).

As of early April 2016, 13 countries and territories had reported increased numbers of GBS cases, and laboratory confirmation of Zika virus infection in a large proportion of GBS case patients has led to preliminary scientific consensus that Zika virus can cause GBS (29). Our 2 travel-related cases of GBS after Zika virus infection are therefore not surprising. The incidence rate of 0.24 GBS case per 1000 Zika virus infections in the French Polynesian cohort (4) was lower than the rate of 0.25 to 0.65 case per 1000 patients infected with *Campylobacter jejuni*, which is known to be associated with GBS (30). Although abundant surveillance data (27) and case reports (31, 32) have been published with regard to neurologic disorders associated with Zika virus infection, the precise dimension of the problem in the Americas awaits clarification as addi-

tional systematically collected population-level data become available.

Given GeoSentinel's role as a sentinel network, 2 cases identified by participating sites merit specific mention: the first local Zika virus transmission in Costa Rica (13) in a traveler exposed in December 2015, and the first identified importation of Zika virus into Denmark in a traveler exposed in January 2016.

In 2015, about 9.9 million travelers departed from Brazilian airports located in or near areas conducive to year-round Zika virus transmission (33). These travelers arrived mainly in the Americas (65%) and Europe (27%). Although travel volume to and from South America, Central America, and the Caribbean is highest for the United States, our case series of travelers with Zika virus disease is skewed toward European travelers, likely because of more ready access to testing in large European centers and differences in the proportion of ill travelers captured by GeoSentinel sites in Europe relative to North America. At the time of this analysis, no commercial diagnostic test for Zika virus existed. In the United States, diagnostic testing was restricted to specific categories of patients by protocol (such as pregnant women and patients with GBS) and was available only through the CDC (34). Consequently, relatively few U.S. patients could be tested and availability of test results was delayed.

We found regional differences in diagnostic practices, specifically in the use of plaque-reduction neutralization testing to confirm Zika virus infection (which was performed only in North America). Differences in the sensitivity and specificity of available molecular diagnostic tests have recently been highlighted (35). Furthermore, urine and semen samples remain PCR-positive longer than serum, which has important implications for case detection (7, 11, 36). In the future, standardization of diagnostic strategies and quality control for tests will be important for Zika virus disease surveillance (35).

All of our case patients were presumed to have been infected through the bite of infected mosquitos, but new evidence has documented alternative routes of Zika virus transmission, including through sexual contact (semen, cervical or vaginal secretions, anal sex, or oral sex), blood transfusion, organ transplantation, laboratory exposure, and potentially breast milk and saliva (11, 14, 36–47). These nonvector transmission routes, especially through unprotected sex, increase the potential for Zika virus spread and the complexity of the public health challenge to prevent infections. The situation demands continuously updated travel medicine advisories as new evidence becomes available. Infective Zika virus has been documented in semen at least 69 days after onset of symptoms (47), and viral RNA has been detected by PCR as long as 188 days after onset of symptoms (48). Until recently (49), all men with Zika virus in their semen had symptomatic disease and, in most reported cases, sexual intercourse occurred while they were actively symptomatic (14) or immediately before symptom onset (36). However, with the first reported case of possible sexual transmission from an asymptomatic male to his female partner (49), current recommendations for prevention of sexual transmission of Zika virus take on additional urgency (36). This includes a need to counsel patients who are planning travel to areas with ongoing Zika virus transmission about effective methods to prevent unintended pregnancy and consistent use of their chosen method. In addition, couples who desire pregnancy should be made aware before travel of the recommended time to wait (currently 6 months per the World Health Organization) before attempting conception upon their return.

Given the increasing evidence of different methods of sexual transmission of Zika virus, travelers to regions with ongoing Zika virus transmission should be counselled on the need for and duration of barrier contraception to limit onward sexual transmission of the virus. Avoidance of the primarily daytime-biting *Aedes* mosquitos is critical to preventing introduction of Zika virus to home countries, including after travel if the traveler is returning to a country where competent vectors are present. Wearing long-sleeved, permethrin-impregnated clothing and using insect repellents are essential preventive measures. DEET (*N*,*N*-diethyl-3-methylbenzamide) at concentrations of 20% or greater shows the highest efficacy and longest protection (up to 10 hours) against *Aedes* species but requires repeated applications per the product directions (50). For daytime use, sunscreen should be applied first, and when this is absorbed, repellent should then be applied. Insect repellent containing DEET is considered safe during the second and third trimesters of pregnancy, and 1 controlled study found no adverse outcomes in infant survival, growth, or development at birth or at age 1 year (51). Limited data exist on the safety of insect repellents in the first trimester (52), but the risk for severe neurologic insult should be weighed against the potential risk to the fetus of repellent exposure through maternal absorption.

Most important, preparation and advising of travelers visiting areas with ongoing Zika virus transmission should address the risk for GBS and pregnancy complications, including severe birth defects and fetal death. Discussion should be individualized, should target specific groups, and should follow evolving national and international guidelines (**Table 3**) (36, 53, 54).

Because GeoSentinel sites are specialized travel and tropical medicine centers, our data are not representative of all travelers with Zika virus disease. All case patients were travelers and were presumed to have been infected by mosquitos; we were unable to elucidate whether sexual transmission may have been responsible for their infections. The sample was limited by bias toward large centers and those that had early access to diagnostic tests (European centers) and by country-specific patterns and volumes of travel. Our series has documented a higher proportion of serious cases, which illustrates a referral bias compared with estimates of microcephaly (27) and GBS (4) from other populations. Certain symptoms were recorded voluntarily and were not based on a mandatory list, leading to potential underreporting of some symptoms. Furthermore, variation in the sensitivity of different Zika vi-

Table 3. Interim Recommendations for Travelers to Prevent Zika Virus Spread via Sexual Transmission and Zika Virus–Associated Pregnancy and Fetal Complications*

Demographic Group	Recommendation
Persons with risk for pregnancy and fetal complications (36, 53, 54)	
Pregnant women	Avoid travel to areas with active Zika virus circulation. If travel cannot be avoided, talk to a health care provider before travel and optimize use of antivector measures.
Partners of pregnant women	Sexual partners of pregnant women living in or returning from areas where local transmission of Zika virus is known to occur should practice safe sex or abstain from sexual activity for the duration of the pregnancy.
Preconception planning	
Men	The WHO and the CDC advise that symptomatic and asymptomatic men with possible Zika virus exposure or returning from areas with active Zika virus circulation should practice safe sex for 6 mo.
Women	The WHO advises that symptomatic and asymptomatic women with possible Zika virus exposure or returning from areas with active Zika virus circulation should wait ≥6 mo before attempting conception.†
Reducing risk for sexual transmission in persons not planning conception	
Men	The WHO and the CDC advise that symptomatic and asymptomatic men with possible Zika virus exposure or returning from areas with active Zika virus circulation should adopt safe-sex practices for ≥6 mo.
Women	The WHO advises that symptomatic and asymptomatic women with possible Zika virus exposure or returning from areas with active Zika virus circulation should adopt safe-sex practices for ≥6 mo.‡
Selected interim recommendations for Zika virus testing from the CDC (53, 54)	
Pregnant women not residing in an area with active Zika virus transmission	Testing is recommended for pregnant women with possible exposure to Zika virus.
Symptomatic returning travelers or other possible Zika virus exposure	Men and women with possible Zika virus exposure who are planning conception and have Zika virus infection–like symptoms should be tested.

CDC = Centers for Disease Control and Prevention; WHO = World Health Organization.
* Numbers in parentheses are references.
† The CDC currently advises that women with possible Zika virus exposure should wait ≥8 wk after symptom onset or last possible exposure before attempting conception.
‡ The CDC currently advises that women with possible Zika virus exposure should adopt safe-sex practices for ≥8 wk after symptom onset or last possible exposure.

rus PCR assays may have resulted in false-negative results among the clinically suspect cases (35). Finally, GeoSentinel data cannot be used to calculate disease rates or risks because of the lack of a representative denominator of all travelers to specified destinations.

The strength of this case series is that it surveyed Zika virus infections in a large number of multinational international travelers. These systematically collated and analyzed data describe the dynamics of a large infectious disease outbreak and its effect on global travelers, including the role of travelers as sentinels of Zika virus circulation. We also highlight the critical need for high-quality, widely available, standardized diagnostic tests for Zika virus infection.

The complicated cases described in this series, including 3 pregnancies with adverse outcomes, 2 GBS cases, and 1 patient with immune-mediated thrombocytopenia, emphasize the urgency and relevance of careful pretravel advice for persons planning travel to countries with ongoing Zika virus transmission. Because Zika virus infection may be transmitted via nonvector routes (43), clinicians need to be aware and recognize this possibility in nonendemic countries. Timely updates of public health messages can guide clinicians who advise travelers before and after travel. Concise, frequently updated messaging is also important for the public, especially with regard to sexual and nonvector Zika virus transmission. The presence of transmission-competent *Aedes* mosquitos in parts of the United States and Europe and the recent local transmission in Miami, Florida, call for diligent vector control and vector and disease surveillance (55, 56).

From Boston University School of Public Health, Boston Medical Center, Boston University School of Medicine, and Harvard Medical School, Boston, Massachusetts; Centers for Disease Control and Prevention and Emory University, Atlanta, Georgia; Mount Auburn Hospital, Cambridge, Massachusetts; University of Amsterdam, Amsterdam, the Netherlands; University of Zürich Centre for Travel Medicine, WHO Collaborating Centre for Travellers' Health, Epidemiology, Biostatistics and Prevention Institute, Zürich, Switzerland; Harbor Hospital, Rotterdam, the Netherlands; Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, PROSICS Barcelona, Barcelona, Spain; Karolinska University Hospital, Stockholm, Sweden; Groupe Hospitalier Pitié-Salpêtrière, UPMC University, Paris, France; Bronx-Lebanon Hospital Center and Icahn School of Medicine at Mount Sinai, Bronx, New York; Charité-Universitätsmedizin Berlin, Berlin, Germany; Geneva University Hospitals, Geneva, Switzerland; Institute of Tropical Med-

icine, Antwerp, Belgium; Toronto General Hospital, University of Toronto, and Public Health Ontario Laboratories, Toronto, Ontario, Canada; Aix-Marseille University, Marseille, France; Johns Hopkins School of Medicine, Baltimore, Maryland; Alberta Children's Hospital, University of Calgary, Calgary, Alberta, Canada; Monash University, Melbourne, Victoria, Australia; McGill University, Montreal, Quebec, Canada; Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France; Pontificia Universidad Católica de Chile, Santiago, Chile; University Medical Center Hamburg-Eppendorf, Hamburg, Germany; Sheba Medical Center, Tel Hashomer, and the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; Heidelberg University, Heidelberg, Germany; Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore; and Umeå University, Umea, Sweden.

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Requests for Single Reprints: Davidson H. Hamer, MD, Center for Global Health & Development, Boston University School of Public Health, Crosstown 3rd Floor, 801 Massachusetts Avenue, Boston, MA 02118; e-mail, dhamer@bu.edu.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Dr. Hamer: Center for Global Health & Development, Boston University School of Public Health, Crosstown 3rd Floor, 801 Massachusetts Avenue, Boston, MA 02118.
Ms. Barbre: Task Force for Global Health, 325 Swanton Way, Decatur, GA 30030.
Dr. Chen: Travel Medicine Center, Mount Auburn Hospital, 330 Mount Auburn Street, Cambridge, MA 02138.
Drs. Grobusch and Goorhuis: Center for Tropical & Travel Medicine, University of Amsterdam, Meibergdreef 9, PO Box 226600, Amsterdam 1100DD, the Netherlands.
Dr. Schlagenhauf: Zurich University Centre for Travel Medicine, WHO Collaborating Centre for Travellers' Health, Epidemiology, Biostatistics and Prevention Institute, Hirschengraben 84, Zurich CH-8001, Switzerland.
Dr. van Genderen: Havenziekenhuis Travel Clinic Haringvliet, 72 TG, Rotterdam 3011, the Netherlands.
Dr. Molina: Anexos 6a Planta, Hospital General Vall d'Hebron, PO Vall d'Hebron, 119 Barcelona 08035, Spain.
Dr. Asgeirsson: Department of Infectious Diseases, Karolinska University Hospital, Stockholm SE-141 86, Sweden.
Dr. Kozarsky: Department of Medicine, Division of Infectious Diseases, Emory University, 550 Peachtree Street, Medical Office Tower, 7th Floor, Atlanta, GA 30308.
Dr. Caumes: Service des Maladies Infectieuses et Tropicales, Hôpital Pitié-Salpêtrière, 47-83 Bld de l'hôpital, Paris cedex 13 75651, France.
Dr. Hagmann: Division of Pediatric Infectious Diseases, Bronx-Lebanon Hospital Center, 1650 Selwyn Avenue, #2C, Bronx, NY 10457.
Dr. Mockenhaupt: Institute of Tropical Medicine and International Health, Charité Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany.
Dr. Eperon: Division of Tropical and Humanitarian Medicine, Geneva University Hospitals, Rue Gabrielle-Perret-Gentil 4, 1211 Genève 14, Switzerland.
Dr. Barnett: Maxwell Finland Laboratory for Infectious Diseases, Boston Medical Center, 670 Albany Street, 6th Floor, Boston, MA 02118.
Dr. Bottieau: Department of Clinical Sciences, Institute of Tropical Medicine, 155 Nationalestraat, Antwerp 2000, Belgium.
Dr. Boggild: Tropical Disease Unit, Toronto General Hospital, 200 Elizabeth Street, 13EN-1350, Toronto, Ontario M5G 2C4, Canada.
Dr. Gautret: Unité de Recherche en Maladies Infectieuses et Tropicales Emergentes (URMITE) UMR63, CNRS 7278, IRD 198, INSERM 1095, Aix Marseille Université, Faculty of Medicine, 27 bd Jean Moulin, 13005 Marseille, France.
Dr. Hynes: Johns Hopkins University School of Medicine, Geographic Medicine Center, Division of Infectious Diseases, 1503 Jefferson Street, Suite 114, JHU-SOM-DOM, Baltimore, MD 21205.
Dr. Kuhn: Alberta Children's Hospital, 2888 Shaganappi Trail NW, Calgary, Alberta T3B 6A8, Canada.
Mr. Lash and Drs. Cetron and Esposito: Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333.
Dr. Leder: Victorian Infectious Diseases Service, Royal Melbourne Hospital, Grattan Street, Parkville, Victoria 3050, Australia.
Dr. Libman: J.D. MacLean Center for Tropical Diseases, Royal Victoria Hospital, 1001 boul. Décarie Room E05.1830, Montreal, Quebec H4A 3J1, Canada.
Dr Malvy: Service des maladies infectieuses et tropicales, Centre Hospitalier Universitaire, Place Amélie-Raba-Léon, Bordeaux cedex 33075, France.
Dr. Perret: Centro de Enfermedades, Tropicales y Salud del Viajero, Pontificia Universidad Católica de Chile Marcoleta, 391 Santiago 3ER PISO, Chile.
Dr. Rothe: University Medical Centre Hamburg Eppendorf, Department of Medicine, Division of Infectious Diseases and Tropical Medicine, Bernhard-Nocht-Klinik, Bernhard Nocht Strasse 74, Hamburg D-20359, Germany.
Dr. Schwartz: The Center of Geographical Medicine, Department of Internal Medicine "C", Sheba Medical Center, Tel HaShomer Ramat Gan, Israel.
Dr. Wilder-Smith: Lee Kong Chian School of Medicine, Nanyang Technological University, Novena Campus, 11 Mandalay Road, Singapore, 308232.

Author Contributions: Conception and design: D.H. Hamer, M.P. Grobusch, P. Schlagenhauf, F.P. Mockenhaupt, E. Schwartz, M.S. Cetron, D.H. Esposito.
Analysis and interpretation of the data: D.H. Hamer, K.A. Barbre, L.H. Chen, M.P. Grobusch, P. Schlagenhauf, A. Goorhuis, P.J.J. van Genderen, I. Molina, S.H. Hagmann, F.P. Mockenhaupt, E.D. Barnett, E. Bottieau, A.K. Boggild, N.A. Hynes, M. Libman, C. Perret, E. Schwartz, A. Wilder-Smith, M.S. Cetron, D.H. Esposito.
Drafting of the article: D.H. Hamer, L.H. Chen, M.P. Grobusch, P. Schlagenhauf, I. Molina, S.H. Hagmann, F.P. Mockenhaupt, G. Eperon, R.R. Lash, C. Perret, A. Wilder-Smith, D.H. Esposito.
Critical revision of the article for important intellectual content: D.H. Hamer, L.H. Chen, M.P. Grobusch, P. Schlagenhauf, A. Goorhuis, P.J.J. van Genderen, I. Molina, H. Asgeirsson, P.E. Kozarsky, E. Caumes, S.H. Hagmann, F.P. Mockenhaupt, E.D. Barnett, E. Bottieau, A.K. Boggild, P. Gautret, S. Kuhn, K. Leder, M. Libman, D.J.M. Malvy, C. Perret, C. Rothe, E. Schwartz, A. Wilder-Smith, M.S. Cetron, D.H. Esposito.
Final approval of the article: D.H. Hamer, K.A. Barbre, L.H. Chen, M.P. Grobusch, P. Schlagenhauf, A. Goorhuis, P.J.J. van Genderen, I. Molina, H. Asgeirsson, P.E. Kozarsky, E. Caumes, S.H. Hagmann, F.P. Mockenhaupt, G. Eperon, E.D. Barnett, E. Bottieau, A.K. Boggild, P. Gautret, N.A. Hynes, S. Kuhn, R.R. Lash, K. Leder, M. Libman, D.J.M. Malvy, C. Perret, C. Rothe, E. Schwartz, A. Wilder-Smith, M.S. Cetron, D.H. Esposito.
Provision of study materials or patients: L.H. Chen, M.P. Grobusch, P. Schlagenhauf, P.J.J. van Genderen, I. Molina, H. Asgeirsson, P.E. Kozarsky, E. Caumes, S.H. Hagmann, F.P. Mockenhaupt, G. Eperon, E.D. Barnett, P. Gautret, N.A. Hynes, K. Leder, M. Libman, D.J.M. Malvy, C. Perret, C. Rothe, E. Schwartz.
Statistical expertise: F.P. Mockenhaupt.
Obtaining of funding: D.H. Hamer, A. Wilder-Smith, M.S. Cetron.
Administrative, technical, or logistic support: D.H. Hamer, P. Schlagenhauf, F.P. Mockenhaupt, M.S. Cetron.
Collection and assembly of data: L.H. Chen, M.P. Grobusch, P. Schlagenhauf, A. Goorhuis, P.J.J. van Genderen, I. Molina, S.H. Hagmann, F.P. Mockenhaupt, G. Eperon, E.D. Barnett, E. Bottieau, A.K. Boggild, P. Gautret, N.A. Hynes, S. Kuhn, K. Leder, M. Libman, C. Rothe, E. Schwartz, D.H. Esposito.

Appendix: Additional Members of the GeoSentinel Surveillance Network

Additional members of the GeoSentinel Surveillance Network who contributed data but did not author this article are Susan Anderson, MD (Stanford, California); Jan Hacek, MD (Vancouver, British Columbia, Canada); Kevin Kain, MD (Toronto, Ontario, Canada); Rogelio Lopez-Velez, MD, PhD (Madrid, Spain); Carsten Schade, MD (Aarhus, Denmark); and Henry Wu, MD (Atlanta, Georgia).

Appendix Table. U.S. Council of State and Territorial Epidemiologists' Interim Zika Virus Infection Case Definition*

Clinical criteria†

A person with ≥1 of the following:
- Acute onset of fever (measured or reported)
- Maculopapular rash
- Arthralgia
- Conjunctivitis
- Complication of pregnancy
  - Fetal loss in a mother with compatible illness and/or epidemiologic risk factors; or
  - In utero findings of microcephaly and/or intracranial calcifications with maternal risk factors
- Guillain–Barré syndrome not known to be associated with another diagnosed etiology

Probable case

Meets clinical criteria and
- Resides in or has recently traveled to an area with ongoing Zika virus transmission or
- Has direct epidemiologic linkage to a person with laboratory evidence of recent Zika virus infection (e.g., sexual contact, in utero or perinatal transmission, blood transfusion, organ transplantation) or
- Association in time and place with a confirmed or probable case

And meets the following laboratory criteria:
- Positive Zika virus–specific IgM antibodies in serum or CSF and
- Negative dengue virus–specific IgM antibodies and
  - No neutralizing antibody testing performed or
  - <4-fold difference in neutralizing antibody titers between Zika virus and dengue or other flaviviruses endemic to the region where exposure occurred.

Confirmed case

Meets clinical criteria and

Has laboratory evidence of recent Zika virus infection by:
- Detection of Zika virus by culture; viral antigen; or viral ribonucleic acid in serum, CSF, tissue, or other specimen (e.g., amniotic fluid, urine, semen, or saliva) or
- Zika virus IgM antibodies in serum or CSF with Zika virus neutralizing antibody titers 4-fold or greater than neutralizing antibody titers against dengue or other flaviviruses endemic to the region where exposure occurred.

CSF = cerebrospinal fluid.
* Reference 18.
† Used for definition of clinically suspect case patient in the current series.